25 ORGANIC SYNTHESIS

Student Learning Outcomes

[C-12-D-109 to C-12-D-115]

- Explain the concept of organic synthesis and functional group interconversions.
- Identify organic functional groups using the reactions in this progression grid.
- Predict properties and reactions of organic molecules based on functional group presence.
- Devise multi-step synthetic routes for preparing organic molecules.
- Analyze a given synthetic route in terms of type of reaction and reagents used for each step of it, and possible by-products.
- Explain the concept of retro-synthesis and its application in organic synthesis.
- Describe the use of artificial intelligence tools in designing organic molecules which may have the potential to be used as medicine (Halicin can be used as an example).

INTRODUCTION

The study of organic chemistry is organized around functional groups. Although millions of organic compounds are known, there are only a handful of functional groups and each one serves to define a family of organic compounds. Functional group is a part of organic compound where most of the reactions occur. In organic synthesis we design different possible ways to build a target molecule from simpler easily available components. Functional groups play a central role in designing a synthesis. They enable chemists to predict and control the reactions which ultimately lead to the desired product. Identifying a functional group present in a compound can help to predict the properties of the compound. This information is crucial for the development of new organic products, as well as to ensure the purity and composition of the products such as medicines and food additives.

25.1 SYNTHESIS AND RETROSYNTHESIS

Before we start preparing an organic compound, it is important to understand the chemical reactions, the reagents, and the conditions required to complete each step to guarantee successful formation of the target molecule.

Most organic compounds can be prepared by a number of different routes and criteria is required to select the best route. A good synthesis of a substance involves the conversion of cheap and easily available starting materials to the desired product adopting a route which involves the least number of steps and gives a high overall yield.

A large variety of organic reactions that can be used in organic synthesis are known. They can be categorized as whether they bring about functional group interconversions (FGI) or a carbon-

carbon bond formation. Carbon-carbon bond formation reactions are particularly important because the basic strategy of synthesis is to assemble the target molecule from simple and smaller starting materials.

25.1.1 Synthesis

In synthesis, the target molecule is prepared starting from simple commercially available compounds. It may involve many steps or transformations to reach the final target molecule. For example, primary aliphatic amine can be prepared in a single step by treating a haloalkane with ammonia.

$$R—CH_2—Cl + NH_3 \xrightarrow{CCl_4} R—CH_2—NH_2 + HCl$$

Since haloalkane is not easily available rather it is prepared from an alcohol which is more easily available as a starting material. The synthesis of an alkyl amine may be completed in two steps.

$$R—CH_2—OH \xrightarrow{SOCl_2} R—CH_2—Cl \xrightarrow{NH_3} R—CH_2—NH_2 + HCl$$

25.1.2 Retrosynthesis

It is exactly the opposite of the synthesis. It involves the breaking down of the target molecule into less complicated, simpler and more readily available compounds which can serve as starting material. Retrosynthesis involves the disconnection approach.

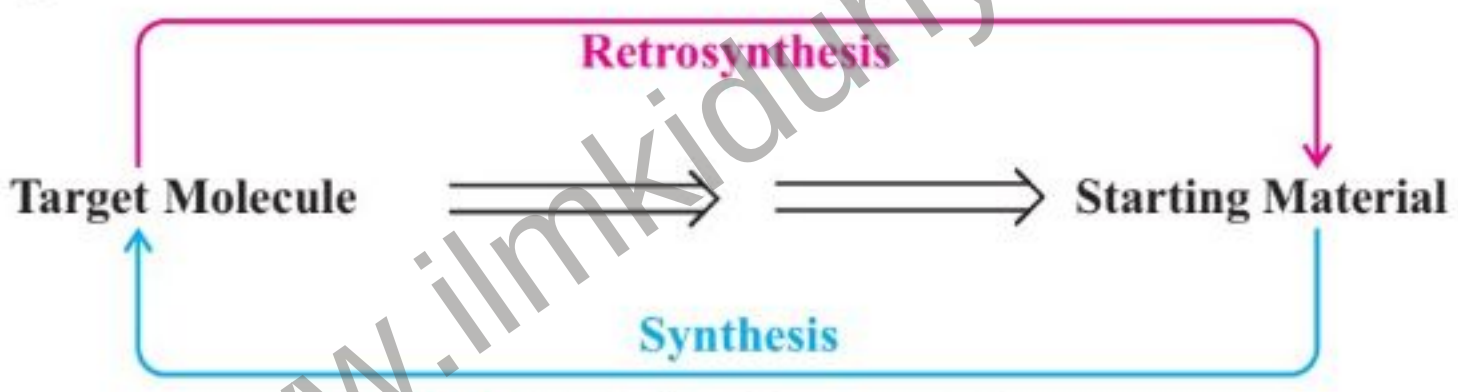


Figure 25.1. Synthesis and retrosynthesis routes

In retrosynthesis, those bonds of the target molecule are disconnected that result in a considerable structural simplification. Following a series of disconnections, we shall eventually arrive at simple, easily available starting materials.

Simple terminology used during retrosynthesis

- **Retrosynthetic arrow** is an open-ended arrow and denoted by $\Longrightarrow$.
- **Target Molecule (TM)** is the molecule which is to be prepared by disconnection.
- **Disconnection** is a process which involves the imaginary breaking down of the TM progressively into simpler starting materials.
- **Synthons** are fragments of the target molecule which are generated by a disconnection. They are often an ionic species and represent the building blocks for the synthesis.
- **Synthetic Equivalent (SE)** is a reagent used to carry out the function of a synthon which cannot be used itself because it is usually unstable.
- **Functional Group Interconversion (FGI)** is the conversion of one functional group into another to reach the target molecule.

- **Retrosynthetic Tree** is a diagram showing all possible disconnections and synthons from the target molecule to starting materials.

Figure 25.2 shows all the terminologies in a single scheme.

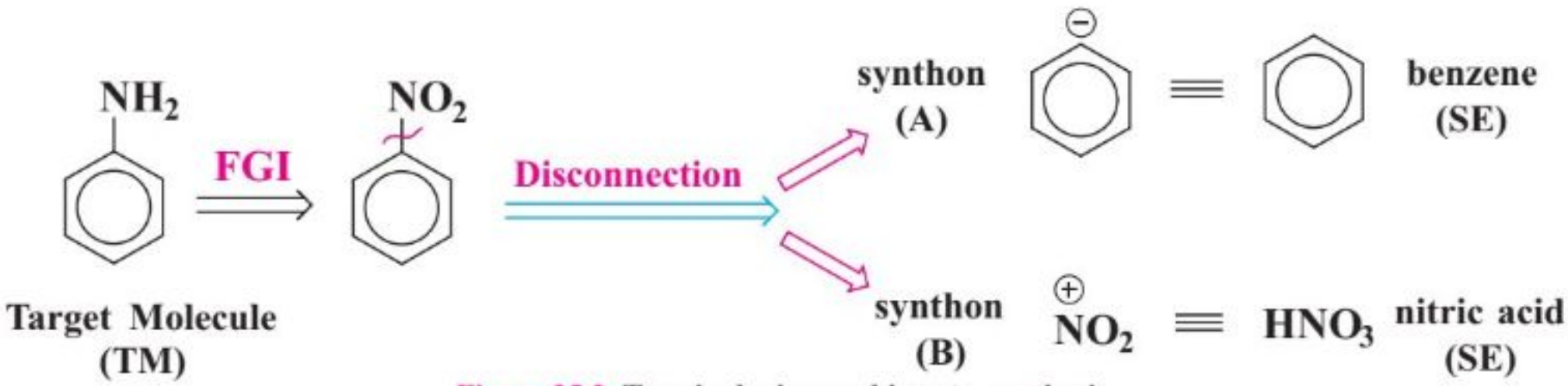


Figure 25.2. Terminologies used in retrosynthesis

Functional Group Interconversion

FGI is a phenomenon to change a functional group into another functional group, required for synthesis of a specific of compound. FGI has a crucial role to play in designing routes which lead to target molecules. Simple starting materials can be converted to more complex target molecules using FGI as building blocks. FGI not only allows to create the carbon skeleton of the target molecule but also select the route to be adopted for this purpose.

The interconversions of functional groups have been studied in detail in earlier chapters and a summary of these interconversions is given in **Figure 25.3 and 25.4**.

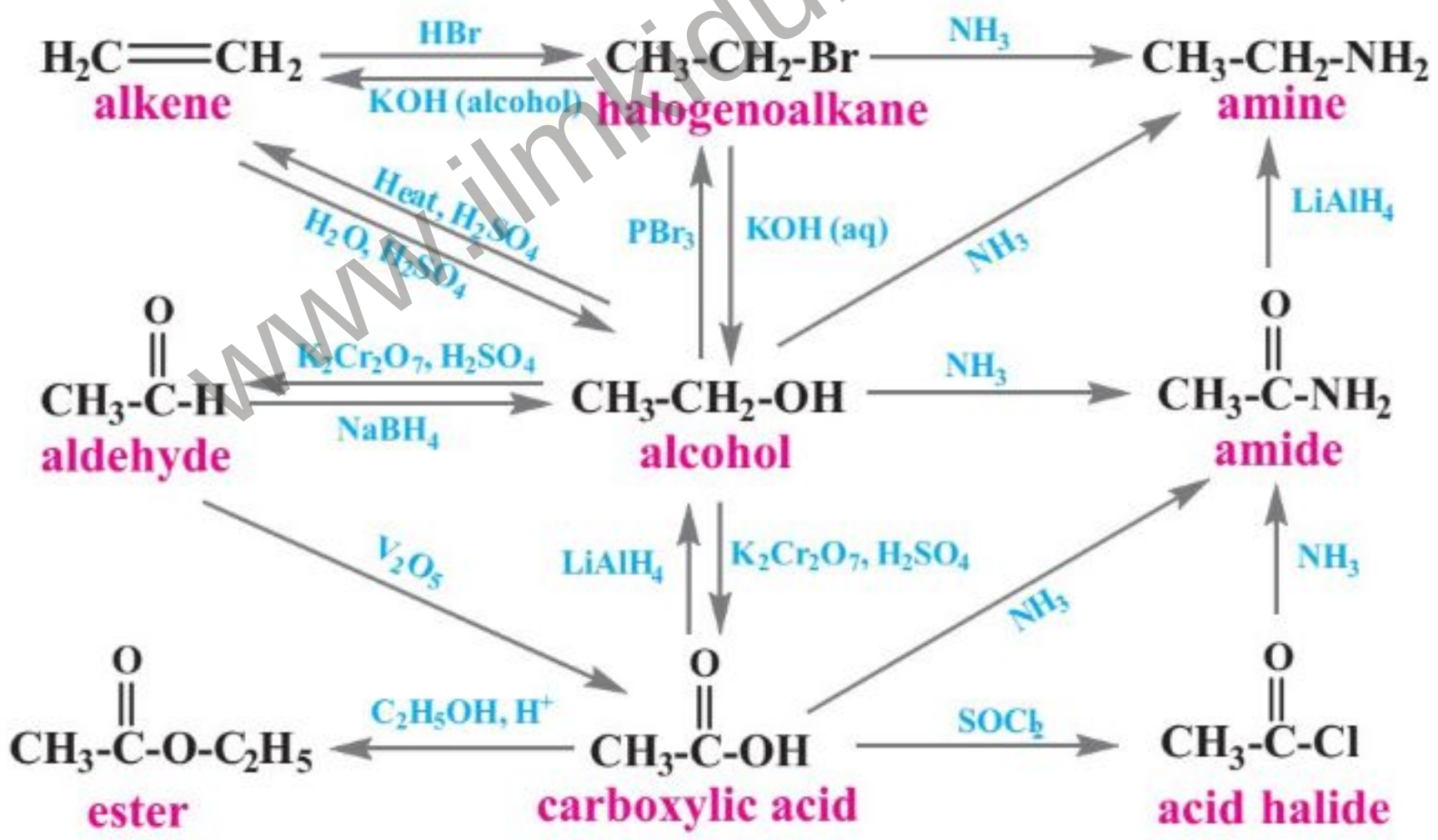


Figure 25.3. Functional group interconversion in aliphatic organic compounds

Quick Check 25.1

i. Why aldehydes and ketones undergo nucleophilic addition reaction readily?

ii. Convert a carboxylic acid to its anhydride.

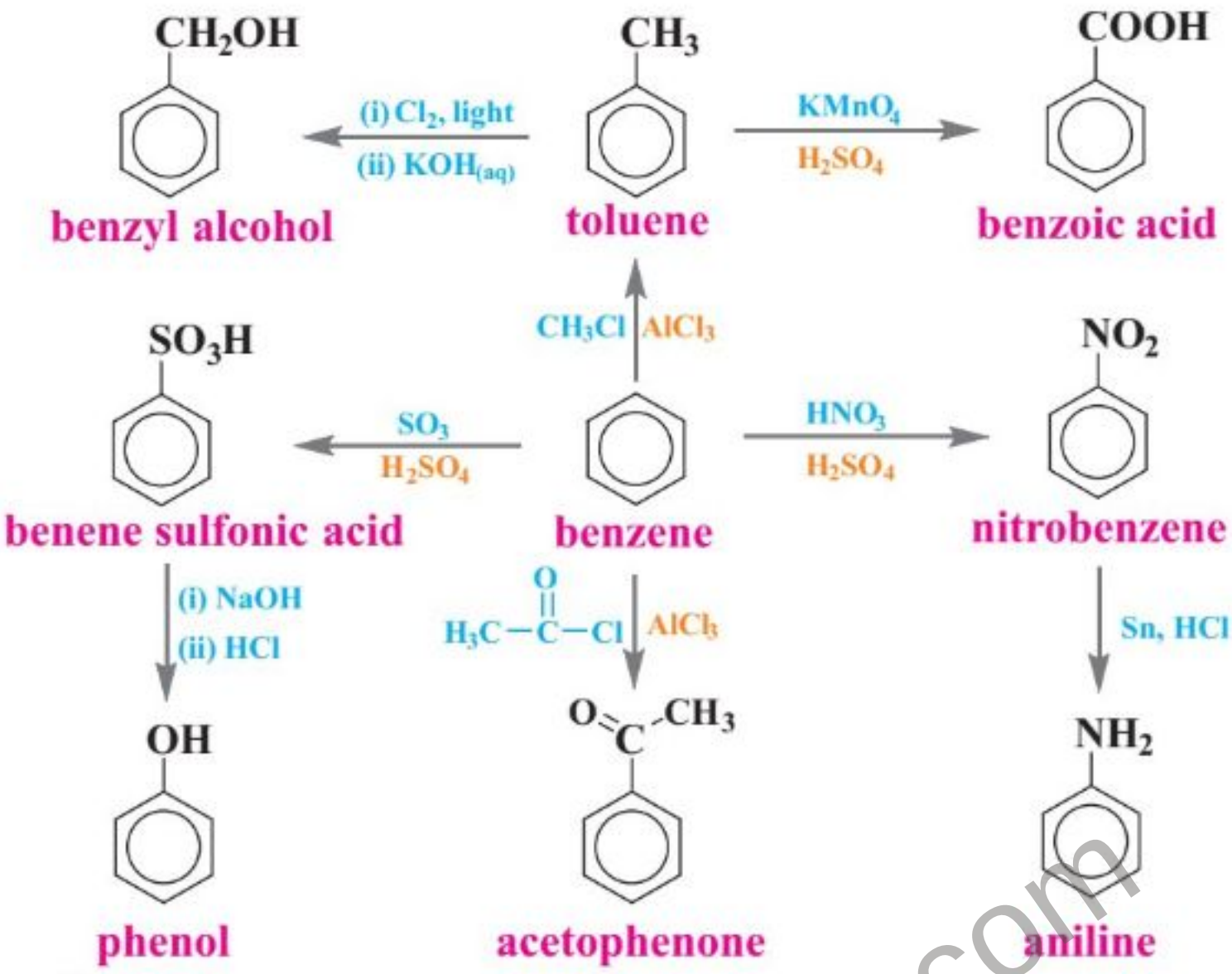


Figure 25.4. Functional group interconversion in aromatic organic compounds

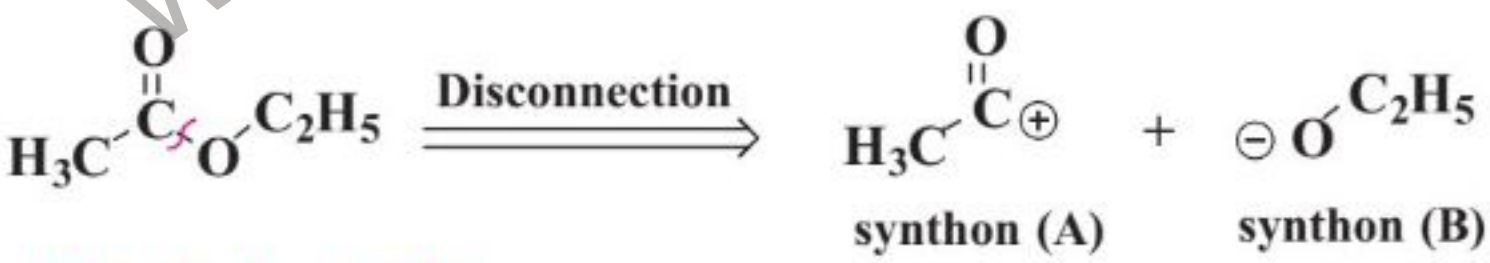
25.2 RETROSYNTHESIS AND SYNTHESIS OF SOME COMPOUNDS

Example 25.2.1 $CH_3COOC_2H_5$ (ethyl acetate, TM)

Retrosynthetic tree

Step I Disconnection

Disconnection at the position indicated will enable us to get synthon A and synthon B whose synthetic equivalents are also shown. While selecting synthetic equivalent molecules thus obtained, they should undergo reaction to give the target molecule.



synthon (A) **synthon (B)**

Step II Synthetic Equivalents (SE)

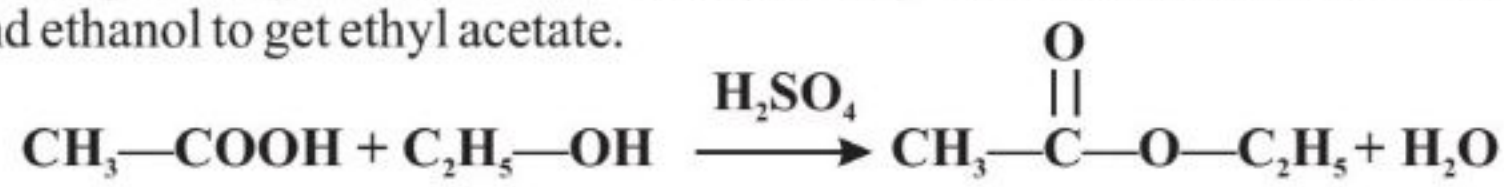
These synthons were neutralized to get synthetic equivalents i.e., benzene and nitric acid molecule.

synthon (A) | **acetic acid (SE)** | **synthon (B)** | **ethanol (SE)**

For our target molecule ethyl acetate, the disconnection followed by neutralization yields acetic acid and ethanol as simpler staring materials to synthesize the TM.

Synthesis of TM (ethyl acetate)

Here we can design the synthesis of our TM by a very familiar esterification reaction between acetic acid and ethanol to get ethyl acetate.

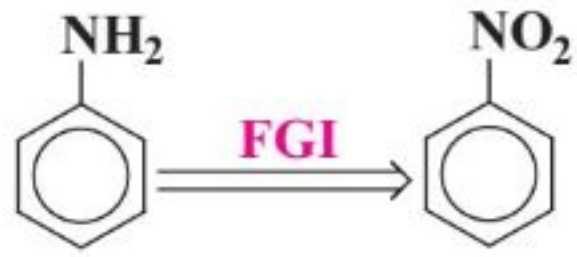


Example 25.2.2 C_6H_5-NH_2 **(aniline, TM)**

Retrosynthetic tree

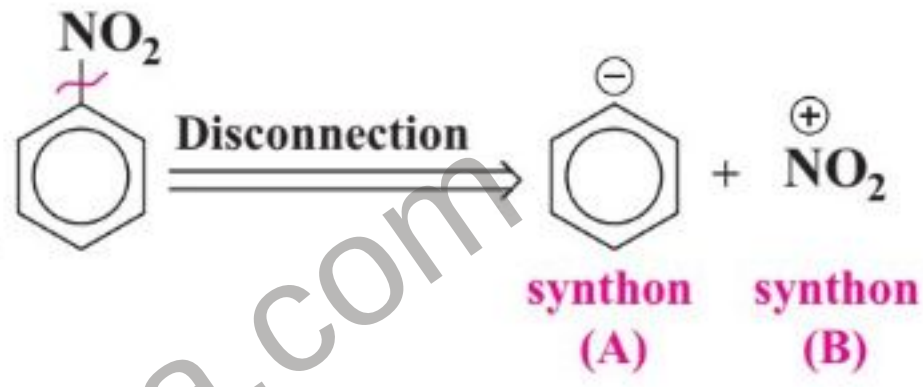
Step I Functional group interconversion

First step of retrosynthesis here is FGI, where amino group (NH_2) is converted into nitro (NO_2) group. Because it is easy to attach nitro group on benzene by electrophilic substitution, rather than amino group by nucleophilic substitution.



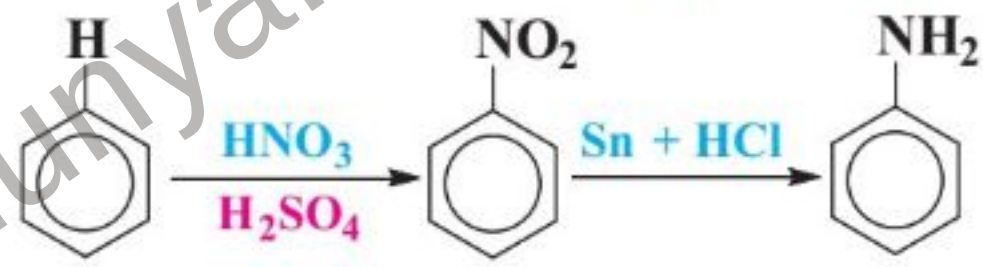
Step II Disconnection

In second step the disconnection of nitrobenzene was done from C—N bond, which created synthons of aryl anion ($C_6H_5^-$) and nitronium (NO_2^+) cation.



Step III Synthetic Equivalents (SE)

These synthons were neutralized to get synthetic equivalents i.e., benzene and nitric acid molecule.

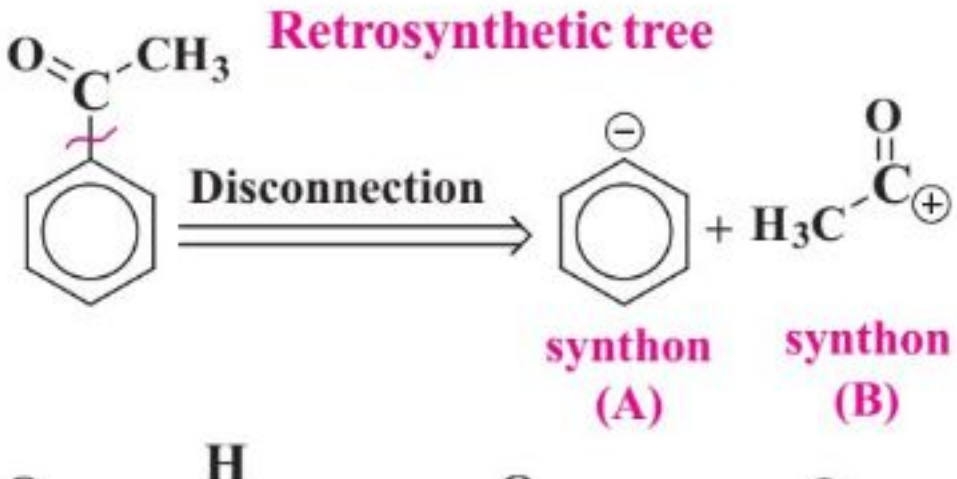


Example 25.2.3 $C_6H_5COCH_3$ **(acetophenone, TM)**

Retrosynthetic tree

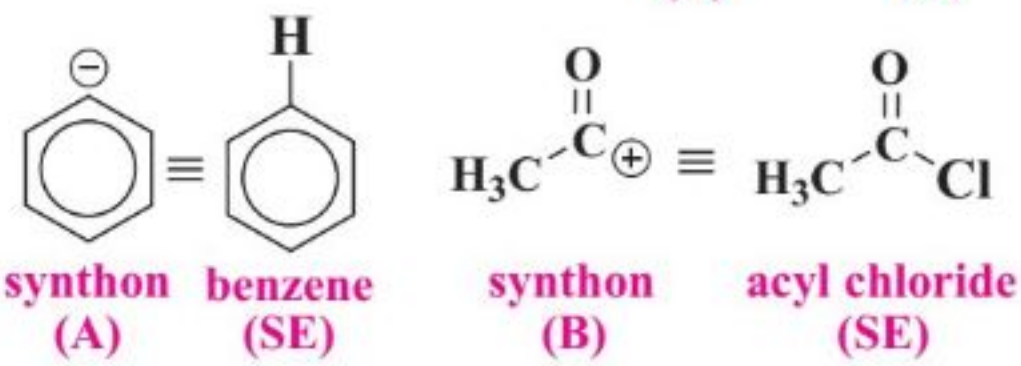
Step I Disconnection

In first step the disconnection of acetophenone (TM) was done from C—C bond, which created synthons of aryl anion ($C_6H_5^-$) and acylium (CH_3CO^+) cation.



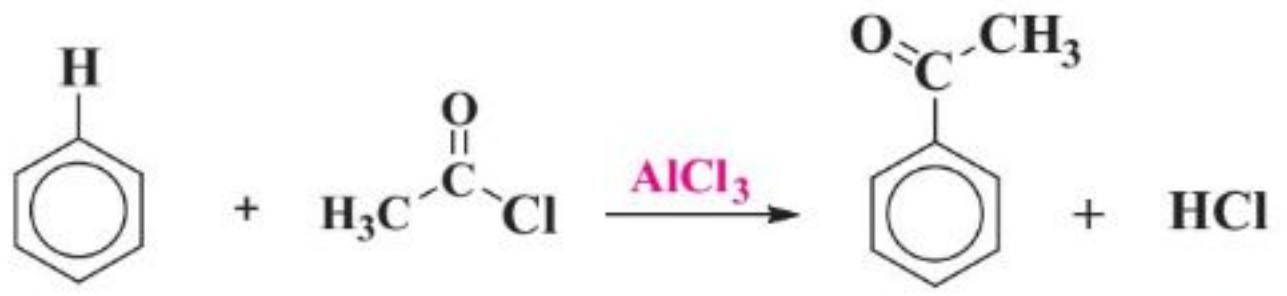
Step II Synthetic Equivalents (SE)

These synthons were neutralized to get synthetic equivalents i.e., benzene and acyl chloride molecule.



Synthesis of TM (acetophenone)

Synthesis of acetophenone can be done by reaction between benzene and acyl chloride, in the presence of $AlCl_3$ as catalyst, using Friedel-Craft acylation process.



MORE INFO Interesting Information

The landmark synthesis of cholesterol was first achieved in early 1950s by two competing groups headed each by Robert Robinson in Oxford and R.B. Woodward at Harvard. These synthetic schemes of cholesterol, had been previously predicted through biological studies.

Quick Check 25.2

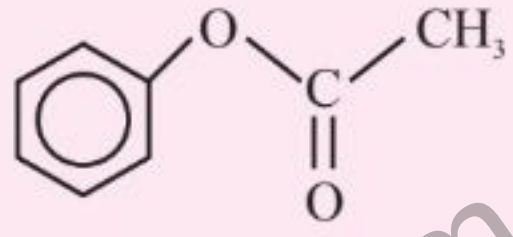
a) Why nitration of benzene is done during synthesis of aniline?

b) Phenyl ethanoate is an important molecule used in synthesis of medicines for hepatitis and various infection.

i) Draw its retrosynthetic tree.

ii) Write structures of its synthetic equivalents.

iii) Design its linear synthesis.

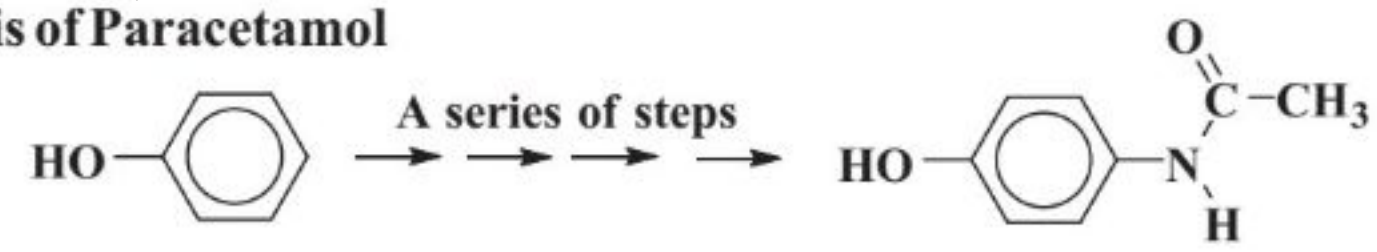


25.3 SYNTHESIS OF PHARMACEUTICAL PRODUCTS

One of the most important applications of retrosynthesis is in pharmaceutical product synthesis. There are hundreds of valuable medicinal compounds, which look very complex in their structure, but if they are disconnected properly and efficiently, we can approach to very simple and commonly available starting materials. This is the beauty of organic synthesis, that it makes the highly complex and terrifying structure, look so simple and achievable after a series of efficient retrosynthetic steps. In the following we will discuss synthesis of some common pharmaceutical products.

Example 25.3.1 Paracetamol (TM)

Direct Synthesis of Paracetamol

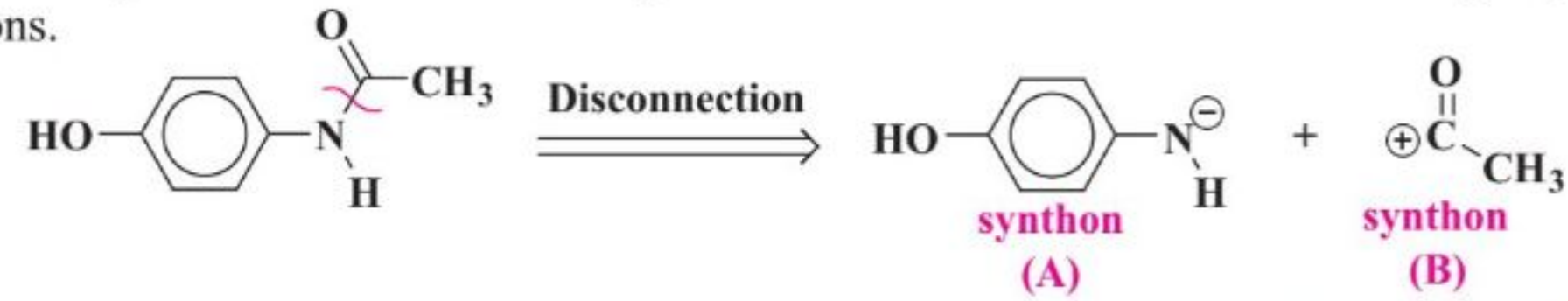


It can be seen that direct synthesis of paracetamol requires a series of steps. This series of steps can be decoded by its retrosynthesis as follows,

Retrosynthesis of Paracetamol

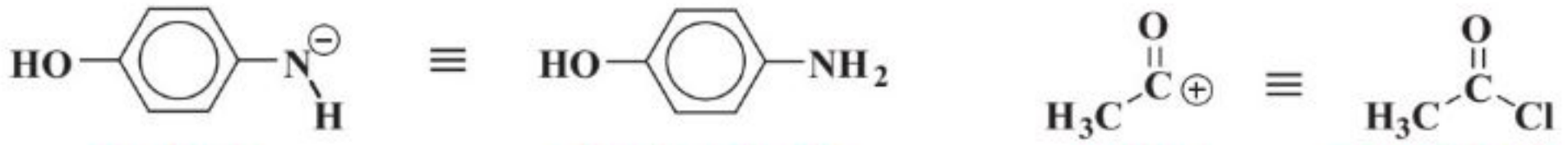
Step I Disconnection

The first step is the disconnection of paracetamol from C—N bond in amide group to get synthons.



Step II Synthetic Equivalents (SE)

These synthons were neutralized to get synthetic equivalents i.e., 4-aminophenol and acyl chloride molecule.



synthon (A) | 4-aminophenol (SE) | synthon (B) | acyl chloride (SE)

The bond is broken at the position indicated because the synthetic equivalents of the resulting synthons are well known to react through a nucleophilic addition-elimination reaction.

Step III Functional group interconversion

FGI has been done because it is easy to prepare p-nitrophenol and it can then be reduced to p-aminophenol.

4-aminophenol | 4-nitrophenol

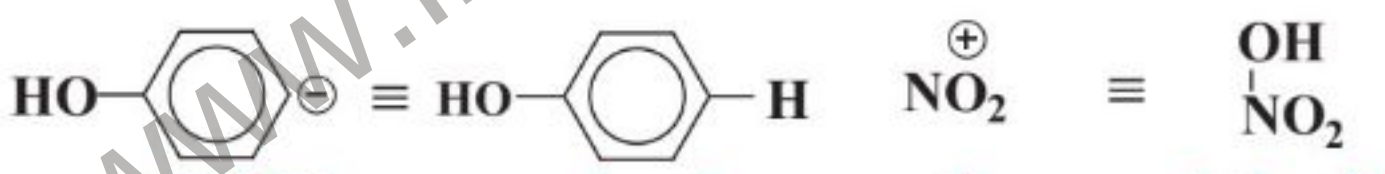
Step IV Disconnection

Then disconnection of 4-aminophenol was done from C—N bond, which created synthons of 4-hyrodxy aryl anion ($C_6H_5^-$) and nitronium (NO_2^+) cation.

synthon (A) | synthon (B)

Step V Synthetic Equivalents (SE)

These synthons were neutralized to get synthetic equivalents i.e., benzene and nitric acid molecule.



synthon (A) | phenol (SE) | synthon (B) | nitric acid (SE)

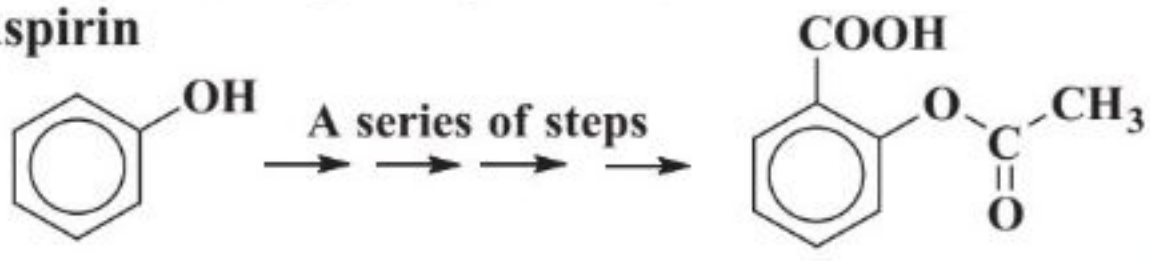
Synthesis of Paracetamol

Paracetamol will then be synthesized according to the following scheme.

phenol (SM) | Paracetamol (TM)

Example 25.3.2 **Aspirin (Acetylsalicylic Acid) TM**

Direct Synthesis of Aspirin



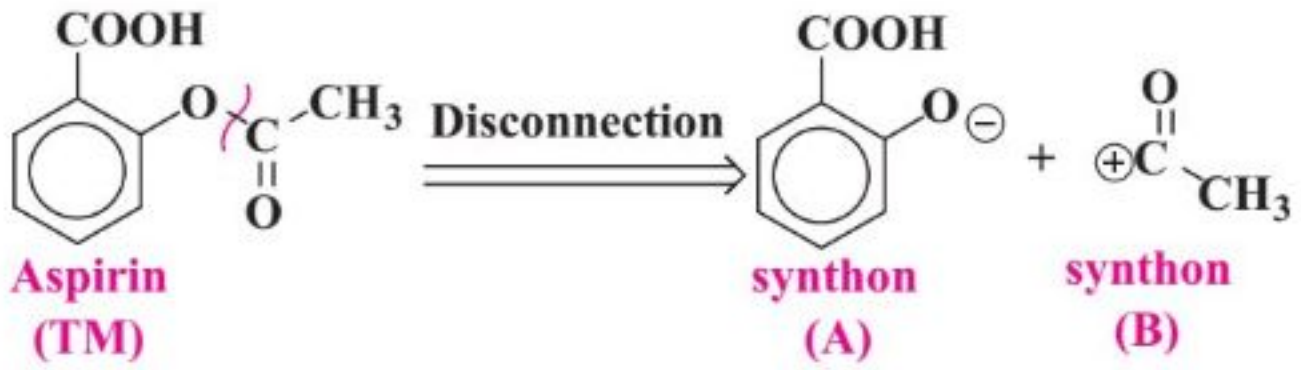
Just like Paracetamol the direct synthesis of Aspirin also requires a series of steps. By retrosynthesis we can truly find how many and which steps are actually needed to prepare Aspirin from phenol (simple starting material).

Retrosynthesis of Aspirin

Retrosynthetic Tree

Step I Disconnection-I

The first step is the disconnection of Aspirin from C—O bond in ester linkage to get synthons.

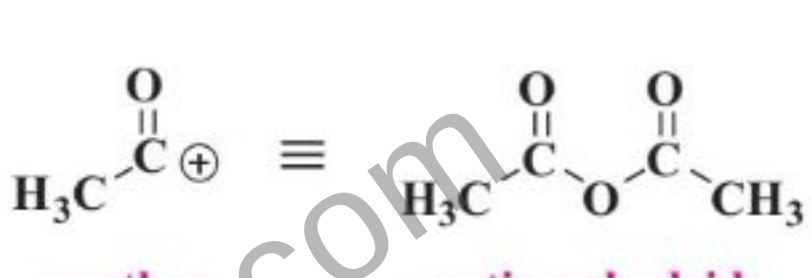


Aspirin (TM) | synthon (A) | synthon (B)

Step II Synthetic Equivalents (SE)

These synthons were neutralized to get synthetic equivalents i.e., salicylic acid and acetic anhydride molecule.

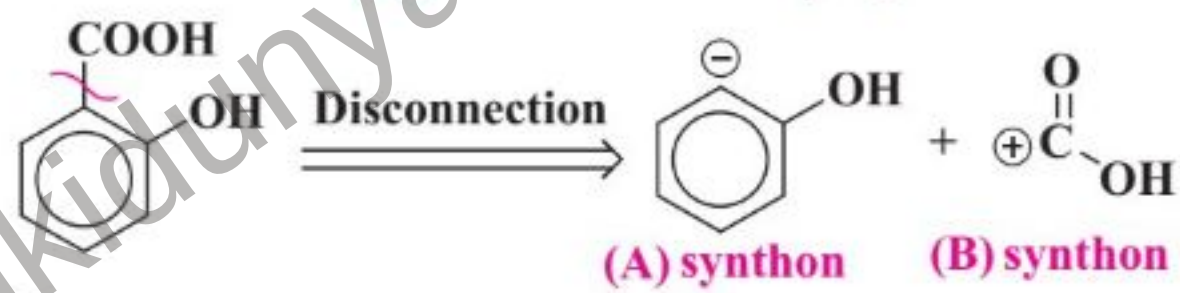
synthon (A) | salicylic acid (SE)



synthon (B) | acetic anhydride (SE)

Step III Disconnection-II

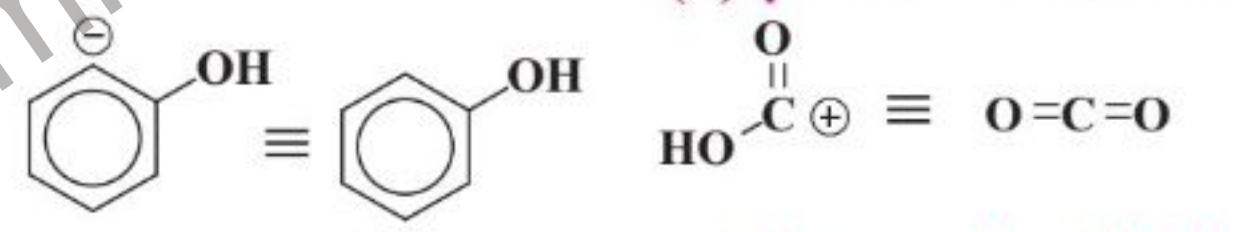
Next disconnection is the C—C bond of carboxylic group.



(A) synthon | (B) synthon

Step IV Synthetic Equivalents (SE)

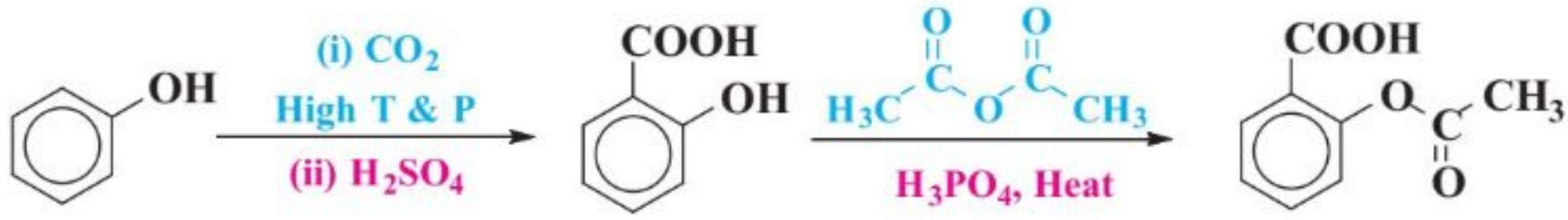
These synthons were neutralized to get synthetic equivalents i.e., phenol and carbon dioxide molecule.



synthon (A) | phenol (SE) | synthon (B) | carbon dioxide (SE)

Synthesis of Aspirin

Aspirin will then be synthesized according to the following scheme.



phenol (SM) | salicylic acid | Aspirin (TM)

Quick Check 25.3

Aspirin and Paracetamol, both are synthesized starting from phenol.

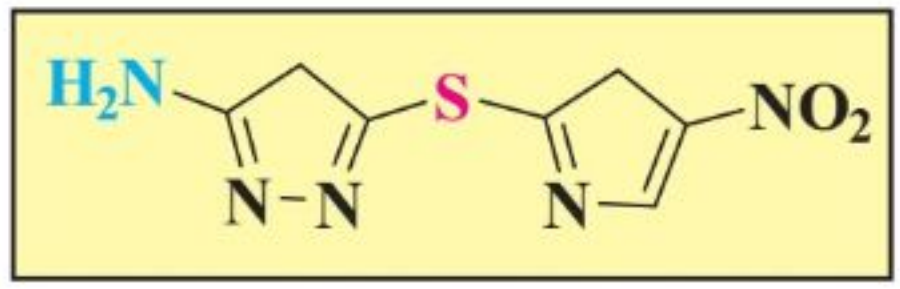
I) What is the overall functional group difference in them?

ii) In synthesis of which FGI (Functional Group Interconversion) is involved?

iii) Which synthon is common in preparation of them? Write down its structure and also mention its most common synthetic equivalent.

25.4 USE OF ARTIFICIAL INTELLIGENCE (AI) IN DRUG DESIGNING

The past few decades have seen the development of very few new antibiotics. Those which have been developed are only slightly different from the existing ones. The methods which are currently used to develop new drugs are very costly, time consuming and are usually limited to a narrow spectrum of chemical activity. We are also facing growing number of cases whereby the prevalent antibiotics become resistant to existing pathogens.



In order to find out a solution to this problem the researchers at MIT (Massachusetts Institute of Technology) designed a machine-learning algorithm to look for chemical features that make molecules effective at killing *E. coli* bacteria. To do so, they applied the model on 2500 molecules and a set of 800 natural products with different structures and a wide range of bioactivities. Once the computer model was applied to these compounds, it picked out one molecule that was predicted to have antibacterial properties with a molecular structure different from the existing antibiotics.

Figure 25.5. Anti bacterial activity of Halicin

Using a different model, the researchers also showed that this molecule would most likely show low toxicity to human cells. Later on, this molecule was named as Halicin and it was tested against a number of bacterial strains isolated from patients. It was found that the new molecule killed many of the world's most problematic disease-causing bacteria which were previously resistant to treatment.

After identifying Halicin, the researchers applied their computer model to screen more than 100 million molecules selected from a database. This screening was completed in only three days, and it selected 23 more such molecules which have different structures from existing antibiotics. Researchers further, found that eight of these molecules showed antibacterial activities and two were particularly powerful. This groundbreaking work points out an altogether different route to discover new organic molecules which may be used as drugs.

MORE INFO Interesting Information

The historic total synthesis of vitamin B_{12} was achieved by R.B. Woodward and A. Eschenmoser in 1972 after over 10 years of collaboration. The total synthesis involved over 100 steps and required 91 post-doctoral researchers and 12 PhD students.

Exercise

Q1. Multiple Choice Questions:

I) After disconnection the components obtained are called:

a) target molecule
b) synthons
c) synthetic equivalents
d) starting material

II) How will you convert the amide functional group (-C≡N) to the amine group?

a) by an oxidation reaction
b) by a reduction reaction
c) by an acid hydrolysis
d) by an addition reaction

III) What does this arrow (⟹) mean in organic chemistry reactions?

a) synthesis
b) Retrosynthesis
c) reversible reaction
d) disconnection

IV) Which reagent you will choose to convert aldehyde group into alcohol?

a) $KMnO_4/H^+$
b) $NaBH_4/H_3O^+$
c) Zn/HCl
d) Na/Liquid NH_3

V) Which reagent is commonly used to oxidize primary alcohol into carboxylic acid?

a) H_2, Pd/C
b) $LiAlH_4$
c) $K_2Cr_2O_7, H_2SO_4$
d) $NaBH_4$

VI) When toluene is treated with $KMnO_4/H_2SO_4$, we obtain:

a) benzyl chloride
b) benzene sulphonic acid
c) benzoic acid
d) acetophenone

VII) Which functional group is formed when a carboxylic acid reacts with an alcohol in the presence of an acid as catalyst?

a) alkane
b) alcohol
c) aldehdye
d) ester

VIII) What is compound A in the given sequence?

$$\textbf{phenol} \xrightarrow{\text{nitration}} \textbf{nitrophenol} \xrightarrow{\text{reduction}} \textbf{aminophenol} \xrightarrow{\text{acetylation}} \textbf{A}$$

a) Aspirin
b) Paracetamol
c) Acetophenone
d) Halicin

IX) In organic synthesis, what is the primary purpose of a 'Functional Group Interconversion' (FGI)?

a) To break the molecule into smaller fragments
b) To increase total number of carbon atoms in molecule
c) To make the molecule more reactive
d) To change the functional group into another to enable a specific reaction

X) The drug 'Halicin' developed by AI work as an:

a) antiviral drung
b) antifungal drug

c) antibiotic drug
d) anticancer drug

Q2. SHORT ANSWER QUESTIONS

a) Differentiate between synthesis and retrosynthesis.
b) How a carboxylic group is converted to an amide group?
c) How synthon and synthetic equivalent are related to each other?
d) Write down the formula of the reagent used for oxidation of organic compounds.
e) Show with equations how alcohol can be converted into amines, alkenes and halogenoalkanes.
f) What is a disconnection in retrosynthesis of a molecule?
g) Mention one useful application of FGI in organic synthesis?
h) Give one method for the reduction of a nitro group ($-NO_2$) to an amino group ($-NH_2$).
i) How a carboxylic group is converted to an alcohol?
j) Design synthesis of 3-chloronitrobenzene and 2-chloronitrobenzene starting from benzene in two steps.

Q3. CONSTRUCTED RESPONSE QUESTIONS

a) Construct the functional group interconversion flow sheet and highlight the important reagents and conversions involved.
b) Construct the retrosynthetic tree for the paracetamol and then design its synthesis.

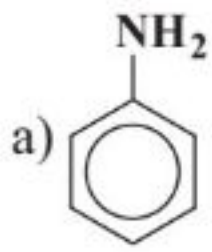
DESCRIPTIVE QUESTIONS

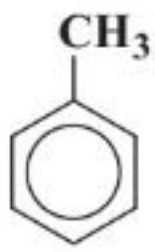
Q4. Give a detailed account of importance of retrosynthesis in organic synthesis.

Q5. Explain the role of halogenoalkanes in retrosynthesis of organic molecules.

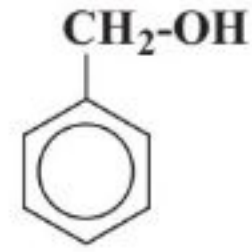
Q6. Construct the retrosynthetic tree for the aspirin and then design its synthesis.

Q7. Design the synthesis of the following molecules starting from benzene.

a) 

b) 

c) 

d) 

Q8. How will you carry out the following conversions?

a) $CH_3—CH_3 \longrightarrow CH_3—COOH$
b) $CH_2=CH_2 \longrightarrow CH_3—CH_2—OH$
c) $CH_3—CH_2—CH_2—Cl \longrightarrow CH_3—CH=CH_2$
d) $CH_3—COOH \longrightarrow CH_3—CH_2—OH$